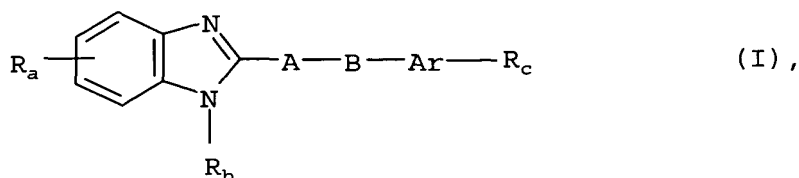


What is claimed is:

1. A method of treating or preventing diseases selected from the group consisting of systemic inflammatory response syndrome (SIRS), sepsis and bacteranemia which comprises administering to a patient in need thereof a therapeutically effective amount of a benzamidazole pharmaceutical composition of general formula (I)



10 wherein

Ar denotes a phenylene or naphthylene group optionally substituted by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C₁₋₃-alkyl or C₁₋₃-alkoxy group,

15 a thienylene, thiazolyne, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C₁₋₃-alkyl group,

A denotes a C₁₋₃-alkylene group,

20

B denotes an oxygen or sulphur atom, a methylene, carbonyl, sulphinyl or sulphonyl group, an imino group optionally substituted by a C₁₋₃-alkyl group wherein the alkyl moiety may be mono- or disubstituted by a carboxy group,

25

R_a denotes a R₁-CO-C₃₋₅-cycloalkyl group wherein

R₁ denotes a C₁₋₃-alkoxy, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group, wherein in each case the alkyl moiety may be substituted by a carboxy group,

5 a 4- to 7-membered cycloalkyleneimino or cycloalkenyleneimino group which may be substituted by one or two C₁₋₃-alkyl groups, while an alkyl substituent may simultaneously be substituted by a hydroxy, C₁₋₃-alkoxy, carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-amino, carboxy-C₁₋₃-alkylaminocarbonyl,
 10 N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-aminocarbonyl, carboxy-C₁₋₃-alkylaminocarbonylamino, 1-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino, 3-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino or 1,3-di-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino group,

15 a 4- to 7-membered cycloalkyleneimino group substituted by a hydroxy group,

20 a 5- to 7-membered cycloalkyleneimino group optionally substituted by a C₁₋₃-alkyl group, to which a phenyl ring is fused via two adjacent carbon atoms,

a morpholino, piperazino, N-(C₁₋₃-alkyl)-piperazino, pyrrolino, 3,4-dehydro-piperidino or pyrrol-1-yl group,

25 a R₂-CX-C₃₋₅-cycloalkyl group wherein

R₂ denotes a phenyl, naphthyl or monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C₁₋₃-alkyl group, while the 6-membered
 30 heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally

substituted by a C₁₋₃-alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C₁₋₃-alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms and the abovementioned alkyl substituent may be substituted by a carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino or N-(C₁₋₃-alkyl)-carboxy-C₁₋₃-alkylamino group, and

X denotes an oxygen atom, a C₁₋₃-alkylimino, C₁₋₃-alkoxyimino, C₁₋₃-alkylhydrazino, di-(C₁₋₃-alkyl)-hydrazino, C₂₋₄-alkanoylhydrazino, N-(C₁₋₃-alkyl)-C₂₋₄-alkanoylhydrazino or C₁₋₃-alkylidene group each of which may be substituted by a carboxy group in the alkyl or alkanoyl moiety or in the alkyl and alkanoyl moiety,

a C₁₋₃-alkyl or C₃₋₅-cycloalkyl group substituted by an imidazole or imidazolone group, wherein

the imidazole ring may be substituted by a phenyl or carboxy group and by one or two C₁₋₃-alkyl groups or by one, two or three C₁₋₃-alkyl groups, while the substituents may be identical or different and one of the abovementioned alkyl substituents may simultaneously be substituted by a carboxy group or in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

the imidazolone ring may be substituted by a C₁₋₃-alkyl group, while the alkyl substituent may be substituted by a carboxy group or in the 2 or 3 position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino, N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

additionally a phenyl or pyridine ring may be fused to the abovementioned imidazole and imidazolone rings via two adjacent carbon atoms,

an imidazolidin-2,4-dion-5-yl group which may be substituted by one or two C₁₋₃-alkyl groups, while simultaneously an alkyl substituent may be substituted by a carboxy group,

5 a C₁₋₄-alkyl group which is substituted

by a C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, HOOC-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, tetrazolyl-C₁₋₃-alkyl-Y₂, R₃NR₄ or R₃NR₄-C₁₋₃-alkyl group and

10 by an isoxazolidinylcarbonyl group optionally substituted by a C₁₋₃-alkyl group, by a pyrrolinocarbonyl, 3,4-dehydro-piperidinocarbonyl, pyrrol-1-yl-carbonyl, carboxy, aminocarbonyl, C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or 4- to 7-membered cycloalkyleneiminocarbonyl group, while in the abovementioned groups the cycloalkyleneimino moiety may be substituted by one or two C₁₋₃-alkyl groups and simultaneously in each case an alkyl moiety or alkyl substituent of the abovementioned
15 C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or cycloalkyleneiminocarbonyl groups may be substituted by a carboxy group, and the remaining hydrogen atoms of the C₁₋₄-alkyl group may be wholly or
20 partly replaced by fluorine atoms, wherein

R₃ denotes a hydrogen atom or a C₁₋₃-alkyl group optionally substituted by a carboxy group and

25 R₄ denotes a hydrogen atom, a C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl-Y₂, carboxy-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl-Y₂, C₁₋₃-alkyl-Y₂ or carboxy-C₁₋₃-alkyl-Y₂ group or

R₃ and R₄ together with the nitrogen atom between them denote a 4- to 7-membered cycloalkyleneimino group optionally substituted by a carboxy,
30 C₁₋₃-alkyl or carboxy-C₁₋₃-alkyl group, wherein

Y_1 denotes a carbon-carbon bond, an oxygen atom, a sulphenyl, sulphinyl, sulphonyl, -NH, -NH-CO or -NH-CO-NH group and

5 Y_2 denotes a carbon-nitrogen bond or a carbonyl, sulphonyl, imino or -NH-CO group, while the carbonyl group of the -NH-CO group is linked to the nitrogen atom of the R_3NR_4 group, and the imino groups mentioned in the definition of the groups Y_1 and Y_2 may each additionally be substituted by a C_{1-3} -alkyl or carboxy- C_{1-3} -alkyl group,

10 a C_{1-3} -alkyl or C_{3-5} -cycloalkyl group substituted by a R_5NR_6 group, wherein

R_5 denotes a hydrogen atom, a C_{1-3} -alkyl, C_{5-7} -cycloalkyl, phenylcarbonyl, phenylsulphonyl or pyridinyl group and

15 R_6 denotes a C_{1-3} -alkyl, carboxy- C_{1-3} -alkyl or carboxy- C_{1-3} -alkylcarbonyl group,

20 a C_{1-3} -alkyl group which is substituted by a C_{2-4} -alkanoyl or C_{5-7} -cyclo-alkanoyl group and by a C_{1-3} -alkyl group substituted by a chlorine, bromine or iodine atom,

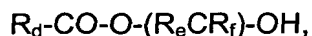
R_b denotes a hydrogen atom or a C_{1-3} -alkyl group and

25 R_c denotes a cyano group or an amidino group optionally substituted by one or two C_{1-3} -alkyl groups, wherein

30 the carboxy groups mentioned in the definition of the abovementioned groups may also be replaced by a group which may be converted *in vivo* into a carboxy group or by a group which is negatively charged under physiological conditions or

the amino and imino groups mentioned in the definition of the abovementioned groups may also be substituted by a group which can be cleaved *in vivo*, while

5 by a group which may be converted into a carboxy group *in vivo* is meant a hydroxymethyl group, a carboxy group esterified with an alcohol wherein the alcoholic moiety is a C₁₋₆-alkanol, a phenyl-C₁₋₃-alkanol, a C₃₋₉-cycloalkanol, while a C₅₋₈-cycloalkanol may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₅₋₈-cycloalkanol wherein a methylene group
 10 in the 3 or 4 position is replaced by an oxygen atom or by an imino group optionally substituted by a C₁₋₃-alkyl, phenyl-C₁₋₃-alkyl, phenyl-C₁₋₃-alkoxycarbonyl or C₂₋₆-alkanoyl group and the cycloalkanol moiety may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₄₋₇-cycloalkenol, a C₃₋₅-alkenol, a phenyl-C₃₋₅-alkenol, a C₃₋₅-alkynol or phenyl-
 15 C₃₋₅-alkynol, with the proviso that no bond to the oxygen atom starts from a carbon atom which carries a double or triple bond, a C₃₋₈-cycloalkyl-C₁₋₃-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms which may additionally be substituted in the bicycloalkyl moiety by one or two C₁₋₃-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of
 20 formula



wherein

25 R_d denotes a C₁₋₈-alkyl, C₅₋₇-cycloalkyl, phenyl or phenyl- C₁₋₃-alkyl group

R_e denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl or phenyl group
 and

30 R_f denotes a hydrogen atom or a C₁₋₃-alkyl group,

by a group which is negatively charged under physiological conditions is meant a tetrazol-5-yl, phenylcarbonylaminocarbonyl, trifluoromethylcarbonylaminocarbonyl, C₁₋₆-alkylsulphonylamino, phenylsulphonylamino, benzylsulphonylamino, trifluoromethylsulphonylamino, C₁₋₆-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, benzylsulphonylaminocarbonyl or perfluoro-C₁₋₆-alkylsulphonylaminocarbonyl group

and by a group which can be cleaved from an imino or amino group *in vivo* is meant a hydroxy group, a benzoyl group optionally mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C₁₋₃-alkyl or C₁₋₃-alkoxy groups, while the substituents may be identical or different, a pyridinoyl group or a C₁₋₁₆-alkanoyl group, a 3,3,3-trichloropropionyl or allyloxycarbonyl group, a C₁₋₁₆-alkoxycarbonyl or C₁₋₁₆-alkylcarbonyloxy group, wherein hydrogen atoms may be wholly or partly replaced by fluorine or chlorine atoms, a phenyl-C₁₋₆-alkoxycarbonyl group, a 3-amino-propionyl group wherein the amino group may be mono- or disubstituted by C₁₋₆-alkyl or C₃₋₇-cycloalkyl groups and the substituents may be identical or different, a C₁₋₃-alkylsulphonyl-C₂₋₄-alkoxycarbonyl, C₁₋₃-alkoxy-C₂₋₄-alkoxy-C₂₋₄-alkoxycarbonyl, R_d-CO-O-(R_dCR_f)-O-CO, C₁₋₆-alkyl-CO-NH-(R_gCR_h)-O-CO or C₁₋₆-alkyl-CO-O-(R_gCR_h)-(R_gCR_h)-O-CO group, wherein R_d to R_f are as hereinbefore defined and

R_g and R_h, which may be identical or different, denote hydrogen atoms or C₁₋₃-alkyl groups,

the tautomers, stereoisomers, mixtures thereof and the salts thereof,

optionally in the form of the pharmaceutically acceptable acid addition salts thereof, as well as optionally in the form of the hydrates or solvates thereof,

for preparing a pharmaceutical composition for the prevention or treatment of diseases from the group consisting of systemic inflammatory response syndrome (SIRS), sepsis and bacteraemia.

- 5 **2.** The method according to claim 1, wherein the benzimidazole used is (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole, optionally in the form of the pharmaceutically acceptable acid addition salts thereof, and optionally in the form of the hydrates or solvates thereof.
- 10
- 3.** The method according to claim 2, wherein the monohydrochloride salt of (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole is used.
- 15 **4.** The method according to claim 1, wherein the condition is selected from the group consisting of SIRS caused by gram-positive pathogens, SIRS caused by gram-negative pathogens, SIRS caused by viruses, SIRS caused by single-cell eukaryotic parasites, SIRS caused by fungi, SIRS without organ failure, SIRS with organ failure, septic shock, septic syndrome, SIRS caused by pancreatitis, SIRS caused by systemic ischaemia, SIRS caused by organ-limited ischaemia, SIRS caused by trauma, SIRS occurring in connection with tumour diseases, SIRS caused by tissue damage, SIRS caused by burns, SIRS occurring after lengthy operations, SIRS as a consequence of organ transplants, SIRS as the result of shock of various kinds, SIRS caused by blood loss, SIRS as the result of cardiovascular failure, SIRS as the result of immuno-mediated organ failure, SIRS as the result of inflammatory reactions, SIRS as the result of treatment with inflammation mediators such as for example tumour necrosis factor alpha and/or beta and/or other cytokines, and also consisting of lung damage, acute lung injury and ARDS (acute respiraotry distress syndrome), acute cardiovascular failure, organ failure after resuscitation, shock, kidney failure, cardiovascular failure,
- 20
- 25
- 30

haematological damage, acidosis and multiple organ dysfunction syndrome (MODS) occurring in connection with SIRS.

- 5 **5.** The method of claim 1, wherein the pharmaceutical composition is intended as an accompanying treatment for bacteraemia.
- 6.** The method of claim 1, wherein the pharmaceutical composition is intended for subcutaneous or parenteral and particularly intravenous administration.
- 10 **7.** The method of claim 1 further comprised of the step of co-administration of an inhibitor of platelet function.
- 8.** The method of claim 7 wherein the inhibitor of platelet function is selected from the list consisting of acetylsalicylic acid, fibrinogen receptor antagonists, inhibitors of ADP-induced aggregation, P₂T receptor antagonists and
15 combined thromboxane receptor antagonists / synthetase inhibitors.
- 9.** The method of claim 1 further comprised of the step of co-administration of a thrombolytically active substance.
20
- 10.** The method of claim 9 wherein the thrombolytically active substance is selected from the list consisting of alteplase, reteplase, tenecteplase, urokinase, staphylokinase and streptokinase.
- 25 **11.** The method of claim 1 further comprised of the step of co-administration of physiological activators and inhibitors of the clotting system and their recombinant analogues.
- 30 **12.** The method of claim 11 wherein the physiological activators and inhibitors of the clotting system are selected from the group consisting of Protein C, recombinant human activated Protein C, TFPI and antithrombin.

13. The method of claim 1 further comprised of the step of co-administration of substances with an antagonistic effect on endotoxins.

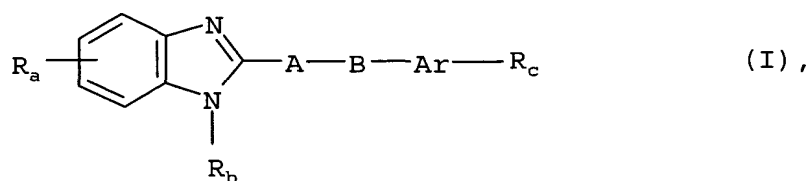
5 14. The method of claim 1 further comprised of the co-administration compounds selected from the list consisting of interleukins, TNF, bradykinin, prostaglandins, cyclooxygenases, NO, platelet activating factor, acetylhydrolases, inflammation inhibitors, immunosuppressant substances, antibiotics and catecholamines

10

15. Pharmaceutical composition comprised of

(a) at least one active substance selected from the group of benzimidazoles of general formula (I)

15



wherein

20 Ar denotes a phenylene or naphthylene group optionally substituted by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C₁₋₃-alkyl or C₁₋₃-alkoxy group,

a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C₁₋₃-alkyl group,

25

A denotes a C₁₋₃-alkylene group,

B denotes an oxygen or sulphur atom, a methylene, carbonyl, sulphinyl or sulphonyl group, an imino group optionally substituted by a C₁₋₃-alkyl group wherein the alkyl moiety may be mono- or disubstituted by a carboxy group,

5 R_a denotes a R₁-CO-C₃₋₅-cycloalkyl group wherein

R₁ denotes a C₁₋₃-alkoxy, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group, wherein in each case the alkyl moiety may be substituted by a carboxy group,

10

a 4- to 7-membered cycloalkyleneimino or cycloalkenyleneimino group which may be substituted by one or two C₁₋₃-alkyl groups, while an alkyl substituent may simultaneously be substituted by a hydroxy, C₁₋₃-alkoxy, carboxy, carboxy-C₁₋₃-alkoxy, carboxy-C₁₋₃-alkylamino, N-(C₁₋₃-alkyl)-

15

N-(carboxy-C₁₋₃-alkyl)-amino, carboxy-C₁₋₃-alkylaminocarbonyl, N-(C₁₋₃-alkyl)-N-(carboxy-C₁₋₃-alkyl)-aminocarbonyl, carboxy-C₁₋₃-alkylaminocarbonylamino, 1-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino, 3-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino or 1,3-di-(C₁₋₃-alkyl)-3-(carboxy-C₁₋₃-alkyl)-aminocarbonylamino group,

20

a 4- to 7-membered cycloalkyleneimino group substituted by a hydroxy group,

25

a 5- to 7-membered cycloalkyleneimino group optionally substituted by a C₁₋₃-alkyl group, to which a phenyl ring is fused via two adjacent carbon atoms,

30

a morpholino, piperazino, N-(C₁₋₃-alkyl)-piperazino, pyrrolino, 3,4-dehydro-piperidino or pyrrol-1-yl group,

a R_2 -CX- C_{3-5} -cycloalkyl group wherein

R_2 denotes a phenyl, naphthyl or monocyclic 5- or 6-membered heteroaryl group optionally substituted by a C_{1-3} -alkyl group, while the 6-membered heteroaryl group contains one, two or three nitrogen atoms and the 5-membered heteroaryl group contains an imino group optionally substituted by a C_{1-3} -alkyl group, an oxygen or sulphur atom or an imino group optionally substituted by a C_{1-3} -alkyl group and an oxygen or sulphur atom or one or two nitrogen atoms and the abovementioned alkyl substituent may be substituted by a carboxy, carboxy- C_{1-3} -alkoxy, carboxy- C_{1-3} -alkylamino or N-(C_{1-3} -alkyl)-carboxy- C_{1-3} -alkylamino group, and

X denotes an oxygen atom, a C_{1-3} -alkylimino, C_{1-3} -alkoxyimino, C_{1-3} -alkylhydrazino, di-(C_{1-3} -alkyl)-hydrazino, C_{2-4} -alkanoylhydrazino, N-(C_{1-3} -alkyl)- C_{2-4} -alkanoylhydrazino or C_{1-3} -alkylidene group each of which may be substituted by a carboxy group in the alkyl or alkanoyl moiety or in the alkyl and alkanoyl moiety,

a C_{1-3} -alkyl or C_{3-5} -cycloalkyl group substituted by an imidazole or imidazolone group, wherein

the imidazole ring may be substituted by a phenyl or carboxy group and by one or two C_{1-3} -alkyl groups or by one, two or three C_{1-3} -alkyl groups, while the substituents may be identical or different and one of the abovementioned alkyl substituents may simultaneously be substituted by a carboxy group or in the 2 or 3 position by an amino, C_{2-4} -alkanoylamino, C_{1-3} -alkylamino, N-(C_{2-4} -alkanoyl)- C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group, and

the imidazolone ring may be substituted by a C_{1-3} -alkyl group, while the alkyl substituent may be substituted by a carboxy group or in the 2 or 3

position by an amino, C₂₋₄-alkanoylamino, C₁₋₃-alkylamino,
N-(C₂₋₄-alkanoyl)-C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, and

5 additionally a phenyl or pyridine ring may be fused to the abovementioned
imidazole and imidazolone rings via two adjacent carbon atoms,

an imidazolidin-2,4-dion-5-yl group which may be substituted by one or two
C₁₋₃-alkyl groups, while simultaneously an alkyl substituent may be
substituted by a carboxy group,

10 a C₁₋₄-alkyl group which is substituted

by a C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, HOOC-C₁₋₃-alkyl-Y₁-C₁₋₃-alkyl, tetrazolyl-
C₁₋₃-alkyl-Y₂, R₃NR₄ or R₃NR₄-C₁₋₃-alkyl group and

15 by an isoxazolidinylcarbonyl group optionally substituted by a C₁₋₃-alkyl
group, by a pyrrolinocarbonyl, 3,4-dehydro-piperidinocarbonyl, pyrrol-1-yl-
carbonyl, carboxy, aminocarbonyl, C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-
aminocarbonyl or 4- to 7-membered cycloalkyleneiminocarbonyl group,
20 while in the abovementioned groups the cycloalkyleneimino moiety may be
substituted by one or two C₁₋₃-alkyl groups and simultaneously in each case
an alkyl moiety or alkyl substituent of the abovementioned
C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl or
cycloalkyleneiminocarbonyl groups may be substituted by a carboxy group,
25 and the remaining hydrogen atoms of the C₁₋₄-alkyl group may be wholly or
partly replaced by fluorine atoms, wherein

R₃ denotes a hydrogen atom or a C₁₋₃-alkyl group optionally
substituted by a carboxy group and

R_4 denotes a hydrogen atom, a C_{1-3} -alkyl- Y_1 - C_{1-3} -alkyl- Y_2 , carboxy- C_{1-3} -alkyl- Y_1 - C_{1-3} -alkyl- Y_2 , C_{1-3} -alkyl- Y_2 or carboxy- C_{1-3} -alkyl- Y_2 group or

5 R_3 and R_4 together with the nitrogen atom between them denote a 4- to 7-membered cycloalkyleneimino group optionally substituted by a carboxy, C_{1-3} -alkyl or carboxy- C_{1-3} -alkyl group, wherein

10 Y_1 denotes a carbon-carbon bond, an oxygen atom, a sulphenyl, sulphinyl, sulphonyl, -NH, -NH-CO or -NH-CO-NH group and

Y_2 denotes a carbon-nitrogen bond or a carbonyl, sulphonyl, imino or -NH-CO group, while the carbonyl group of the -NH-CO group is linked to the nitrogen atom of the R_3NR_4 group, and the imino groups mentioned in
15 the definition of the groups Y_1 and Y_2 may each additionally be substituted by a C_{1-3} -alkyl or carboxy- C_{1-3} -alkyl group,

a C_{1-3} -alkyl or C_{3-5} -cycloalkyl group substituted by a R_5NR_6 group, wherein

20 R_5 denotes a hydrogen atom, a C_{1-3} -alkyl, C_{5-7} -cycloalkyl, phenylcarbonyl, phenylsulphonyl or pyridinyl group and

R_6 denotes a C_{1-3} -alkyl, carboxy- C_{1-3} -alkyl or carboxy- C_{1-3} -alkylcarbonyl group,
25

a C_{1-3} -alkyl group which is substituted by a C_{2-4} -alkanoyl or C_{5-7} -cyclo-alkanoyl group and by a C_{1-3} -alkyl group substituted by a chlorine, bromine or iodine atom,

30 R_b denotes a hydrogen atom or a C_{1-3} -alkyl group and

R_c denotes a cyano group or an amidino group optionally substituted by one or two C_{1-3} -alkyl groups, wherein

5 the carboxy groups mentioned in the definition of the abovementioned groups may also be replaced by a group which may be converted *in vivo* into a carboxy group or by a group which is negatively charged under physiological conditions or

10 the amino and imino groups mentioned in the definition of the abovementioned groups may also be substituted by a group which can be cleaved *in vivo*, wherein

15 by a group which may be converted into a carboxy group *in vivo* is meant a hydroxymethyl group, a carboxy group esterified with an alcohol wherein the alcoholic moiety is a C_{1-6} -alkanol, a phenyl- C_{1-3} -alkanol, a C_{3-9} -cycloalkanol, while a C_{5-8} -cycloalkanol may additionally be substituted by one or two C_{1-3} -alkyl groups, a C_{5-8} -cycloalkanol wherein a methylene group in the 3 or 4 position is replaced by an oxygen atom or by an imino group optionally substituted by a C_{1-3} -alkyl, phenyl- C_{1-3} -alkyl, phenyl- C_{1-3} -alkoxycarbonyl or
20 C_{2-6} -alkanoyl group and the cycloalkanol moiety may additionally be substituted by one or two C_{1-3} -alkyl groups, a C_{4-7} -cycloalkenol, a C_{3-5} -alkenol, a phenyl- C_{3-5} -alkenol, a C_{3-5} -alkynol or phenyl- C_{3-5} -alkynol,

25 with the proviso that no bond to the oxygen atom starts from a carbon atom which carries a double or triple bond, a C_{3-8} -cycloalkyl- C_{1-3} -alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms which may additionally be substituted in the bicycloalkyl moiety by one or two C_{1-3} -alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula

30 $R_d\text{-CO-O-(R}_e\text{CR}_f\text{)-OH,}$

wherein

R_d denotes a C_{1-8} -alkyl, C_{5-7} -cycloalkyl, phenyl or phenyl- C_{1-3} -alkyl group

5 R_e denotes a hydrogen atom, a C_{1-3} -alkyl, C_{5-7} -cycloalkyl or phenyl group and

R_f denotes a hydrogen atom or a C_{1-3} -alkyl group,

by a group which is negatively charged under physiological conditions is
 10 meant a tetrazol-5-yl, phenylcarbonylaminocarbonyl,
 trifluoromethylcarbonylaminocarbonyl, C_{1-6} -alkylsulphonylamino,
 phenylsulphonylamino, benzylsulphonylamino,
 trifluoromethylsulphonylamino, C_{1-6} -alkylsulphonylaminocarbonyl,
 phenylsulphonylaminocarbonyl, benzylsulphonylaminocarbonyl or perfluoro-
 15 C_{1-6} -alkylsulphonylaminocarbonyl group

and by a group which can be cleaved from an imino or amino group *in vivo* is
 meant a hydroxy group, a benzoyl group optionally mono- or disubstituted by
 fluorine, chlorine, bromine or iodine atoms, by C_{1-3} -alkyl or C_{1-3} -alkoxy
 20 groups, while the substituents may be identical or different, a pyridinoyl group
 or a C_{1-16} -alkanoyl group, a 3,3,3-trichloropropionyl or allyloxycarbonyl group,
 a C_{1-16} -alkoxycarbonyl or C_{1-16} -alkylcarbonyloxy group, wherein hydrogen
 atoms may be wholly or partly replaced by fluorine or chlorine atoms, a
 phenyl- C_{1-6} -alkoxycarbonyl group, a 3-amino-propionyl group wherein the
 25 amino group may be mono- or disubstituted by C_{1-6} -alkyl or C_{3-7} -cycloalkyl
 groups and the substituents may be identical or different, a
 C_{1-3} -alkylsulphonyl- C_{2-4} -alkoxycarbonyl, C_{1-3} -alkoxy- C_{2-4} -alkoxy-
 C_{2-4} -alkoxycarbonyl, R_d -CO-O- (R_dCR_f) -O-CO, C_{1-6} -alkyl-CO-NH-
 (R_gCR_h) -O-CO or C_{1-6} -alkyl-CO-O- (R_gCR_h) - (R_gCR_h) -O-CO group, wherein R_d
 30 to R_f are as hereinbefore defined and

R_g and R_h , which may be identical or different, denote hydrogen atoms or C_{1-3} -alkyl groups,

the tautomers, stereoisomers, mixtures thereof and the salts thereof, and

5

(b) at least one active substance selected from the group consisting of inhibitors of platelet function such as in particular acetylsalicylic acid, fibrinogen receptor antagonists, inhibitors of ADP-induced aggregation, P_2T receptor antagonists and combined thromboxane receptor antagonists /
 10 synthetase inhibitors, thrombolytically active substances, such as in particular alteplase, reteplase, tenecteplase, urokinase, staphylokinase and streptokinase, physiological activators and inhibitors of the clotting system and their recombinant analogues such as in particular Protein C, recombinant human activated Protein C, TFPI and antithrombin, substances
 15 with an antagonistic effect on endotoxins, interleukins, TNF, bradykinin, prostaglandins, cyclooxygenases, NO, platelet activating factor acetylhydrolases, inflammation inhibitors, immunosuppressant substances, antibiotics and catecholamines

20 **16.** Pharmaceutical composition according to claim 15, comprised of
 (a) (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole, optionally in the form of the pharmaceutically acceptable acid addition salts and optionally in the form of the hydrates or solvates thereof, and

25 (b) a PAF-AH or a PAF-AH derivative.

17. Pharmaceutical kit comprised of at least

(a) (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole, optionally in the
 30 form of the pharmaceutically acceptable acid addition salts and optionally in the form of the hydrates or solvates thereof, and

(b) a PAF-AH or a PAF-AH derivative.

18. Pharmaceutical kit comprised of least

- 5 (a) (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole, optionally in the form of the pharmaceutically acceptable acid addition salts and optionally in the form of the hydrates or solvates thereof, and
- (b) a tumour necrosis factor alpha (TNF-alpha) antagonist.

- 10 **19.** Use of a PAF-AH or a PAF-AH derivative or a TNF-alpha antagonist for preparing a pharmaceutical composition for combined use with a (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole.